Common Drug Review

Pharmacoeconomic Review Report

November 2013

Drug	Saxagliptin (Onglyza)
Indication	Indicated in patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin and a sulfonylurea when dual therapy with these two agents, with diet and exercise, does not provide adequate glycemic control.
Listing request	In combination with metformin and a sulfonylurea when dual therapy with these two agents, with diet and exercise, does not provide adequate glycemic control for whom insulin is not an option.
Manufacturers	Bristol-Myers Squibb Canada and AstraZeneca Canada

This report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). Through the Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary listing recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with *CDR Update — Issue 87*, manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

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ABBREVIATIONS

A1C	glycated hemoglobin
CDR	Common Drug Review
DPP-4	dipeptidyl peptidase-4
ODB	Ontario Drug Benefit

EXECUTIVE SUMMARY OF THE PHARMACOECONOMIC SUBMISSION

Saxagliptin (Onglyza) is available as a 5 mg tablet to be taken once daily. It is indicated in combination with metformin and a sulfonylurea when dual therapy with these two drugs, with diet and exercise, does not provide adequate glycemic control. At a confidential price of $[redacted] per tablet ($[redacted] daily), the daily cost of saxagliptin is less than that of sitagliptin ($2.95; 100 mg) but higher than or equal to that of linagliptin ($2.25 to $2.55; 5 mg). Saxagliptin is more expensive than all other oral antidiabetics, including sulfonylureas, thiazolidinediones, and alpha-glucosidase inhibitors.

REVIEW OF THE PHARMACOECONOMIC SUBMISSION

1. INTRODUCTION

Saxagliptin (Onglyza) is an oral antihyperglycemic drug belonging to the dipeptidyl peptidase-4 (DPP-4) inhibitor class. It is indicated for patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin, a sulfonylurea, metformin and a sulfonylurea, or long or intermediate-acting insulin (with or without metformin) when these drugs alone do not provide adequate glycemic control. The recommended dose of saxagliptin is 5 mg once daily for most patients and 2.5 mg once daily for patients with moderate or severe renal impairment (CrCl ≤ 50 mL/min). The manufacturers submitted a confidential price of $[redacted] per 5 mg tablet ($[redacted] per day).

1.1 Cost Comparison Table

The comparator treatments presented in Table 1 have been deemed the appropriate comparators by clinical experts. Comparators may be recommended (appropriate) practice versus actual practice. Comparators are not only restricted to drugs, but may also be devices or procedures. Costs are manufacturers' list prices, unless otherwise specified.

TABLE 1: COST COMPARISON TABLE FOR NON-INSULIN ANTIDIABETIC DRUGS

Drug / Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
Saxagliptin (Onglyza)	2.5 mg 5.0 mg	tab	[redacted][a]	5 mg daily	[redacted]	[redacted]
Dipeptidyl peptidase-4 (DPP-4) inhibitors						
Linagliptin (Trajenta)	5 mg	tab	2.5500	5 mg daily	2.55	931
Sitagliptin (Januvia)	100 mg	tab	2.9527	100 mg daily	2.95	1,078
Biguanides						
Metformin	500 mg 850 mg	tab	0.0587 0.2299[b]	500 mg, three to four times daily	0.18 to 0.23	64 to 86
Glucagon-like peptide-1 (GLP-1) receptor agonist						
Exenatide (Byetta)	1.2 mL 2.4 mL	60-dose pre-filled pen (250 mcg/mL)	149.4100[c]	10 mcg, twice daily	4.98	1,817
Liraglutide (Victoza)	2 × 3 mL 3 × 3 mL (6 mg/mL)	inj	167.0100[c] 250.5100[c]	1.2 mg to 1.8 mg daily	5.57 to 8.35	2,032 to 3,048
Insulin Secretagogues, Sulfonylureas						
Gliclazide (generics)	80 mg	tab	0.0931	80 mg to 320 mg daily (in divided doses if > 160 mg daily)	0.09 to 0.37	34 to 136

Drug / Comparator	Strength	Dosage Form	Price ($)	Recommended Dose	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
Insulin Secretagogues, Sulfonylureas (cont'd)						
Gliclazide long-acting (Diamicron MR)	30 mg 60 mg	ER tab	0.1405 0.2529	30 mg to 120 mg daily	0.14 to 0.51	51 to 185
Glimepiride (generics)	1 mg 2 mg 4 mg	tab	0.4851[b]	1 mg to 4 mg daily	0.49	177
Glyburide (generics)	2.5 mg 5.0 mg	tab	0.0321 0.0574	2.5 mg to 20 mg daily (in divided doses if > 10 mg daily)	0.03 to 0.23	12 to 84
Thiazolidinediones (TZDs)						
Pioglitazone (generics)	15 mg 30 mg 45 mg	tab	0.8133[b] 1.1394[b] 1.7132[b]	15 mg to 45 mg daily	0.81 to 1.71	267 to 625
Rosiglitazone (Avandia)	2 mg 4 mg 8 mg	tab	1.3755[d] 2.1584[d] 3.0865[d]	4 mg to 8 mg daily	2.16 to 3.09	788 to 1,126
Rosiglitazone / metformin (Avandamet)	1 mg / 500 mg 2 mg / 500 mg 4 mg / 500 mg 2 mg / 1,000 mg 4 mg / 1,000 mg	tab	0.6421[d] 1.1611[d] 1.5943[d] 1.2682[d] 1.7337[d]	4 mg /1,000 mg to 8 mg/2,000 mg daily, in divided doses	2.32 to 3.47	847 to 1,266
Alpha-glucosidase inhibitors						
Acarbose (Glucobay)	50 mg 100 mg	tab	0.2682 0.3714	50 mg to 100 mg, three times daily	0.80 to 1.11	294 to 407

ER = extended release; inj = injectable; tab = tablet.
Source: Ontario Drug Benefit (June 2013) prices unless otherwise stated. Prices do not include dispensing fees. A cost comparison of different insulin drugs is presented in Table 6 in Appendix 1.
[a] Manufacturers confidential submission price.
[b] Manitoba Drug Formulary (June 2013).
[c] McKesson Canada wholesale price (June 2013).
[d] Saskatchewan Drug Formulary (June 2013).

2. SUMMARY OF PHARMACOECONOMIC SUBMISSION

The manufacturers submitted a cost-minimization analysis[1] comparing saxagliptin 5 mg to linagliptin 5 mg and sitagliptin 100 mg for patients with type 2 diabetes using third-line therapy, i.e., when dual therapy with metformin and a sulfonylurea, with diet and exercise, does not provide adequate glycemic control. Because no head-to-head trials were available comparing saxagliptin to sitagliptin or linagliptin, the manufacturer performed an indirect treatment comparison (ITC) to compare the effects of each drug in terms of glycated hemoglobin (A1C) control, and to provide justification for undertaking a cost-minimization analysis. The manufacturers' indirect comparison included three placebo-controlled trials investigating the use of saxagliptin (Study 06[2]), linagliptin (Owens et al., 2011[3]), and sitagliptin (Hermansen et al., 2007[4]). The manufacturers' indirect comparison of saxagliptin, linagliptin, and sitagliptin was well-reported and was conducted using an appropriate methodology; a literature search did not identify any relevant missing studies. The results of the indirect comparison suggested that there was no statistically significant difference in A1C control between saxagliptin and either linagliptin or sitagliptin when taken in combination with metformin and a sulfonylurea.

The analysis was conducted from the Canadian public-payer perspective. Only drug acquisition costs were considered (costs do not include a markup); these were obtained from the Ontario Drug Benefit (ODB) (April 2013). Because saxagliptin, linagliptin and sitagliptin are from the same drug class (DPP-4 inhibitors), the manufacturers assumed all other aspects of patient management were equivalent (compliance, adverse events, and discontinuation). For the base-case analysis, the unit drug prices and a weighted average DPP-4 inhibitor cost (i.e., saxagliptin[1], linagliptin, sitagliptin) were derived based on the reported ODB list prices and the utilization of DPP-4 inhibitors within ODB (Table 2).

TABLE 2: LIST PRICES AND MARKET SHARE FROM ODB FOR DPP-4 INHIBITORS

DPP-4	ODB Price[a] ($)	Market Share[b] (%)	Weighted Average DPP-4 Price ($)
Sitagliptin 100 mg	2.95	86.6	2.919
Linagliptin 5 mg	2.55	4.0	
Saxagliptin 5 mg	2.76	9.3	

DPP-4 = dipeptidyl peptidase-4; ODB = Ontario Drug Benefit.
[a] List price was based on the e-formulary price for ODB as of April 22, 2013.
[b] Utilization based on ODB data from IMS Brogan (Q4, 2012).

The unit prices and weighted average DPP-4 inhibitor cost were compared with the proposed saxagliptin unit price confidentially set at $[redacted] per unit (Table 3).

[1] Saxagliptin (Onglyza) is listed in the ODB for diabetic patients on metformin who have inadequate glycemic control and intolerance or contraindication to a sulfonylurea.

TABLE 3: MANUFACTURERS BASE-CASE ANALYSIS RESULTS

Drug	List Price Per Unit[a] ($)	Daily Use	Daily Drug Cost Per Patient ($)	Annual Drug Cost Per Patient ($)	Annual Cost Difference Versus Saxagliptin[b]
Saxagliptin	[redacted]	once daily	[redacted]	[redacted]	--
Sitagliptin	2.95	once daily	2.95	1,076.75	[redacted]
Linagliptin	2.55	once daily	2.55	930.75	[redacted]
DPP-4[c]	2.92	once daily	2.92	1,065.26	[redacted]

[a] List price was based on the e-formulary price for ODB as of April 22, 2013.
[b] For annual cost difference, negative values represent cost savings with use of saxagliptin at price of $[redacted] per unit.
[c] Average cost of DPP-4 inhibitors based on the weighted average of the list price of DPP-4s and ODB reported market share (IMS Brogan 2012). Calculation of annual cost per patient was based on the average weighted cost of DPP-4s ($2.91853) multiplied by 365 days.
Source: Manufacturers Pharmacoeconomic Submission, page 22.

The manufacturers conducted sensitivity analyses to calculate the weighted average DPP-4 inhibitor price by varying utilization of DPP-4 inhibitors (across provinces) (Table 4) and list prices (incorporating either provincial prices or the lowest list price for the DPP-4 on a provincial formulary) (Table 5). For each of the sensitivity analysis, the overall weighted average cost for DPP-4 inhibitors, or DPP-4 unit prices, were compared with the proposed confidential price of $[redacted] per 5 mg units of saxagliptin.

Results of the majority of sensitivity analyses conducted by the manufacturers illustrated that saxagliptin remained cost saving at the submitted price of $[redacted] per 5 mg tablet (Table 4 and Table 5). However, saxagliptin was not cost saving at $[redacted] per 5 mg tablet when compared with the lowest list unit price for linagliptin among provincial formularies ($2.25 in Newfoundland and Labrador, New Brunswick, and British Columbia).

TABLE 4: MANUFACTURERS SENSITIVITY ANALYSIS 1— CANADIAN MARKET SHARE AND FORMULARY LIST PRICES

Drug	Price Per Unit ($)	Daily Use	Daily Drug Cost Per Patient ($)	Annual Drug Cost Per Patient ($)	Annual Cost Difference Versus Saxagliptin[a]
Saxagliptin	[redacted]	once daily	[redacted]	[redacted]	--
DPP-4[b]	2.91	once daily	2.91	1,062.01	[redacted]

DDP-4 = dipeptidyl peptidase-4.
[a] Negative values represent cost savings with the use of saxagliptin at price of $[redacted] per unit. Note that the Canadian average was based on provincial data from BC, Alta., Sask., Ont., NB, NS, and the Newfoundland and Labrador Prescription Drug Program (NLPDP); complete provincial data were unavailable from Man. and PEI. Non-Insured Health Benefits (NIHB Program) data were excluded from this analysis; inclusion of NIHB Program data using either ODB prices or the average Canadian prices as a proxy for the NIHB Program had no impact on the results.
[b] Average cost of DPP-4 inhibitors based on the weighted average of the provincial prices of DPP-4s and provincial reported market share. See details in Appendix 1 for calculations of weighted average price. Calculation of annual cost per patient was based on the average weighted cost of DPP-4s ($2.90962) multiplied by 365 days.
Source: Manufacturers Pharmacoeconomic Submission, page 22.

TABLE 5: MANUFACTURERS SENSITIVITY ANALYSIS 2 — CANADIAN MARKET SHARE AND LOWEST DPP-4 INHIBITOR FORMULARY PRICE

Drug	List Price Per Unit ($)	Daily Use	Daily Drug Cost Per Patient ($)	Annual Drug Cost Per Patient ($)	Annual Cost Difference Versus Saxagliptin[a]
Saxagliptin	[redacted]	once daily	[redacted]	[redacted]	--
Sitagliptin[b]	2.62	once daily	2.62	956.30	–[redacted]
Linagliptin[c]	2.25	once daily	2.25	821.25	[redacted]
DPP-4[d]	2.62	once daily	2.62	955.47	–[redacted]

DPP-4 = dipeptidyl peptidase-4.
[a] For the Annual Cost Difference, negative values represent cost savings with use of saxagliptin at price of $[redacted] per unit.
[b] The lowest list price for sitagliptin within public provincial formularies is $2.62 in Nfld. & Lab.
[c] The lowest list price for linagliptin within public provincial formularies is $2.25 in Nfld & Lab., NB., and BC.
[d] Average cost of DPP-4 based on weighted average price of DPP-4s based on average Canadian market share and lowest formulary cost for DPP-4s across Canada (sitagliptin [$2.62, Newfoundland and Labrador Prescription Drug Program (NLPDP)], linagliptin [$2.25, NLPDP], and saxagliptin [2.76, ODB]). Calculation of the annual cost per patient was based on the average weighted cost of DPP-4s ($2.61773) multiplied by 365 days.
Source: Manufacturers Pharmacoeconomic Submission, page 23.

3. INTERPRETATIONS

3.1 Trial Limitations

The trials included in the indirect comparison presented potential limitations, such as the following:

- the use of surrogate end points (e.g., A1C) to assess the efficacy of saxagliptin
- the relationship between glycemic control as measured by A1C and diabetes-related complications, which remains controversial
- the short trial duration, which may not reflect long-term efficacy and safety.

3.2 Exclusion of Other Relevant Cost Comparators

The manufacturers did not consider oral therapies in other drug classes (meglitinides and alpha-glucosidase inhibitors) that are less expensive than saxagliptin and available for treatment of type 2 diabetes in patients who are not adequately controlled with metformin and sulfonylurea combination. Despite the low utilization of meglitinides and alpha-glucosidase inhibitors in Canada, these classes are still listed under drug plans across Canada and represent valid treatment options.

4. ISSUES FOR CONSIDERATION

The manufacturers are requesting to list saxagliptin for use in patients for whom "insulin is not an option." Without an adequate definition of this, it becomes difficult to appropriately identify eligible patients, and there is a high probability that patients who could be eligible for insulin (mixed or combination), but who are reticent about subcutaneous administration of insulin, may be included. This may have significant implications on the cost-saving capability of saxagliptin, as the manufacturers' submission only compares saxagliptin with other DPP-4 inhibitors.

5. CONCLUSIONS

At the submitted daily cost of $[redacted], the cost of saxagliptin is less than that of sitagliptin ($2.95; 100 mg) but is higher than or equal to that of linagliptin ($2.25 to $2.55; 5 mg). Due to variation in reimbursement prices for DPP-4 across the country, the price of saxagliptin would need to be reduced by at least [redacted]% (to $2.25) to avoid incurring additional costs to plans that cover linagliptin. If saxagliptin were to replace sitagliptin as the most widely used DPP-4 drug, this would generate substantial cost savings for public plans.

APPENDIX 1: COST OF ADDITIONAL COMPARATORS

TABLE 6: COST COMPARISON OF INSULIN DRUGS

Drug/Comparator	Strength	Dosage Form	Price ($)	Cost Per mL ($)
Short-acting insulin (human and analogues)				
Insulin aspart (NovoRapid)	100 U/mL	5 × 3 mL cartridge 10 mL vial	58.29 28.75	3.89 2.88
Insulin glulisine (Apidra)	100 U/mL	5 × 3 mL cartridge 10 mL vial	49.15 24.85	3.28 2.48
Insulin lispro (Humalog)	100 U/mL	5 × 3 mL cartridge 10 mL vial	54.45 27.47	3.63 2.75
Humulin R	100 U/mL	5 × 3 mL cartridge 10 mL vial	43.37 22.10	2.89 2.21
Novolin ge Toronto	100 U/mL	5 × 3 mL cartridge 10 mL vial	40.88 20.83	2.73 2.08
Intermediate-acting human insulin				
Humulin N	100 U/mL	5 × 3 mL cartridge 10 mL vial	43.37 22.10	2.89 2.21
Novolin ge NPH	100 U/mL	5 × 3 mL cartridge 10 mL vial	40.73 20.83	2.72 2.08
Long-acting insulin analogues				
Insulin glargine (Lantus)	100 U/mL	5 × 3 mL cartridge 10 mL vial	91.39 60.52	6.09 6.05
Insulin detemir (Levemir)	100 U/mL	5 × 3 mL cartridge	101.68	6.78
Premixed				
Biphasic insulin aspart 30/70 (NovoMix 30)	100 U/ml	5 × 3 mL cartridge	54.88	3.66
Lispro/lispro protamine 25/75 (Humalog Mix 25)	100 U/mL	5 × 3 mL cartridge	55.09	3.67
Lispro/lispro protamine 50/50 (Humalog Mix 50)	100 U/mL	5 × 3 mL cartridge	54.45	3.63
Humulin 30/70	100 U/mL	5 × 3 mL cartridge 10 mL vial	43.37 22.10	2.89 2.21
Novolin ge 30/70	100 U/mL	5 × 3 mL cartridge 10 mL vial	40.69 20.83	2.71 2.08
Novolin ge 40/60	100 U/mL	5 × 3 mL cartridge	41.67	2.78
Novolin ge 50/50	100 U/mL	5 × 3 mL cartridge	41.67	2.78

Source: ODB (June 2013) prices.

APPENDIX 2: PRICE ANALYSIS

Due to variation in reimbursement prices across Canada, Common Drug Review (CDR) calculated the price reduction that would be required to produce a price of saxagliptin equivalent to the least expensive DPP-4 currently reimbursed by public plans in Canada (linagliptin; $2.25 per day). The price for linagliptin was obtained from the Nova Scotia Pharmacare Programs for being the lowest publicly available price, despite variation in linagliptin prices across Canada. As shown in Table 7, the price of saxagliptin would need to be reduced by [redacted]% from $[redacted] per day to equal that of linagliptin at $2.25 per day, the lowest priced DPP-4 covered in Canada. This would result in a cost savings of up to $[redacted] per patient per year were saxagliptin to be reimbursed at the requested price of $[redacted] per day.

The submitted price for saxagliptin ($[redacted] per day) is already lower than that of sitagliptin ($2.95 per day), another DPP-4 approved in Canada. Sitagliptin is considered to be the most widely used drug of this class among drug plans in Canada, with an approximate market share of 77%. A scenario analysis was conducted whereby saxagliptin was assumed to replace sitagliptin. The price of sitagliptin ($2.95) and utilization data were obtained from the ODB for this analysis. The results in Table 7 indicate the proposed monthly cost savings to the drug plan were saxagliptin to replace sitagliptin.

TABLE 7: CDR ANALYSIS ON PRICE FOR SAXAGLIPTIN

Current Price[a] ($)	Scenario	Reduced Price[b] ($)	% Price Reduction	Range in Savings ($)	Max Savings[c] ($)
[redacted]	Price reduction needed to equal the price of the least expensive DPP-4 (linagliptin)	[redacted]	[redacted]	[redacted] – [redacted]	[redacted]
	Saxagliptin replaces the most widely used DPP-4 (sitagliptin)[d]	NA	NA	NA	[redacted][e]

DDP-4 = dipeptidyl peptidase-4; NA = not applicable.
[a] Manufacturers submitted confidential price.
[b] Dose not include markup or dispensing fees.
[c] Savings per patient per year.
[d] Based on DPP-4 comparator with most units covered by the ODB in June 2013 (IMS Brogan PharmaStat).
[e] Monthly cost savings for ODB.

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